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Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

Date:	September 2, 2014
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EXECUTIVE SUMMARY

In accordance with the FDAAA Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing reports of adverse events and drug utilization data for montelukast in pediatric patients.

Montelukast was first approved in 1998 and is indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older. The approved pediatric labeling is for asthma indication in age 12 months to 14, exercise-induced bronchoconstriction indication in age 6-14, and allergic rhinitis indication: seasonal 2-14 years and perennial 6 months to14 years.

During the examined time period, approximately 40.8 million montelukast prescriptions were dispensed and approximately 8.8 million patients received dispensed prescriptions for montelukast from U.S. outpatient retail pharmacies. Approximately 38% (3.3 million patients) of total patients receiving dispensed prescriptions were pediatric patients aged 0-16 years old; of these, pediatric patients aged 0-1 years, 2-5 years, 6-11 years, and 12-16 years old accounted for approximately 6%, 29%, 47%, and 26%, respectively, of total pediatric patients. "Asthma" and "Allergic Rhinitis" were the two most common diagnoses associated with the use of montelukast for all pediatric age groups. This is consistent with the findings from the FAERS data summary. Although infrequent, off-label indications other than asthma and allergic rhinitis appear to be mentioned for all pediatric age groups.

We reviewed four post-marketing pediatric death cases and 136 non-fatal serious post-marketing cases (with an outcome of life-threatening, hospitalization, or disability) that were received in the FAERS database from March 26, 2012 to September 26, 2013. The pediatric safety profile described in these reports is consistent with the known safety profile of montelukast and the current montelukast label. We did not identify any new safety concerns in children 0 to < 17 years old treated with montelukast.

Overall, the four death cases reported labeled psychiatric adverse events (aggression, behavioral changes, and completed suicide) that are listed in the Warnings and Precautions section of the labeling. The cause of death was unknown in the case of the 2-year-old male (Case # 9006984). The majority of the non-fatal serious adverse events are adequately described in the current labeling. No increased trend in severity or frequency of reporting of labeled events was noted.

The review of the FAERS reports resulted in the identification of a small number of reports for unlabeled events; many events had one single report. Because of the overall small number of reports (compared to 3.3 million pediatric patients receiving dispensed prescriptions for montelukast during this time period), it was difficult to determine whether these reports documented new safety issues. Limitations to case interpretation include incomplete case descriptions or the paucity of clinical data the cases contain, underlying medical disorders, and confounders such as concomitant medications.

Safety concerns have been raised and addressed by the FDA in the past regarding the increased risk of neuropsychiatric adverse events, including suicide and suicide attempts with the use of montelukast. However, there continues to be a lack of well-designed epidemiologic studies that can lead to the quantification of the suicide/suicide attempt risk level among patients using montelukast.

We do not have any recommendations regarding the pediatric population at this time. DPV will continue postmarketing surveillance of all adverse events with the use of montelukast in the pediatric patients.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

This PREA review was triggered because of a prior approval supplemental new drug application that proposes to expand the current indication for prevention of exercise-induced bronchoconstriction (EIB) in patients 15 years of age and older to include patients 6 to 14 years of age. Efficacy for prevention of EIB in patients < 6 years of age has not been established.

Approved Montelukast Dosing by Indication and Age[1]	
Indication	
Age	Dose
Asthma	
≥ 15 years	10 mg
6-14 years	5 mg
2-5 years	4 mg
12-23 months	4 mg
Seasonal Allergic Rhinitis (SAR)	
≥ 15 years	10 mg
6-14 years	5 mg
2-5 years	4 mg
Perennial Allergic Rhinitis (PAR)	
≥ 15 years	10 mg
6-14 years	5 mg
2-5 years	4 mg
6-23 months	4 mg
Exercise Induced Bronchoconstriction	
≥ 15 years	10 mg
6-14 years	5 mg

1.2 SUMMARY OF RELEVANT PREVIOUS DPV SAFETY REVIEWS AND PENDING SUBMISSIONS

(b) (4)

Please see section 3.5.1 for additional analysis on montelukast and enuresis in children. There are no DPV reviews (which include pediatric cases) that are currently pending regulatory action.

1.3 HIGHLIGHTS OF LABELED SAFETY ISSUES[2]

WARNINGS AND PRECAUTIONS

Neuropsychiatric Events

Neuropsychiatric events have been reported in adult, adolescent, and pediatric patients taking montelukast sodium. Post-marketing reports with montelukast sodium use include agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal thinking and behavior (including suicide), and tremor. The clinical details of some post-marketing reports involving montelukast sodium appear consistent with a drug-induced effect.

Patients and prescribers should be alert for neuropsychiatric events. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with montelukast sodium if such events occur.

Eosinophilic Conditions

Patients with asthma on therapy with montelukast sodium may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events have been sometimes associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between montelukast sodium and these underlying conditions has not been established.

ADVERSE REACTIONS

Post-Marketing Experience

Blood and lymphatic system disorders: increased bleeding tendency, thrombocytopenia.
Psychiatric disorders: agitation including aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal thinking and behavior (including suicide), and tremor.
Nervous system disorders: drowsiness, paraesthesia/hypoesthesia, seizures.
Gastrointestinal disorders: diarrhea, dyspepsia, nausea, pancreatitis, vomiting.
Hepatobiliary disorders: Cases of cholestatic hepatitis, hepatocellular liver-injury, and mixed-pattern liver injury.
Musculoskeletal and connective tissue disorders: arthralgia, myalgia including muscle cramps.

Patients with asthma on therapy with montelukast sodium may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events have been sometimes associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients.

PATIENT COUNSELING INFORMATION
Behavior and mood-related changes. Tell your healthcare provider right away if you or your child has any of these symptoms while taking montelukast sodium tablets:
• Agitation including aggressive behavior or hostility
• Attention problems
• Bad or vivid dreams
• Depression
• Disorientation (confusion)
• Feeling anxious
• Hallucinations (seeing or hearing things that are not really there)
• Irritability
• Memory problems
• Restlessness
• Sleep walking
• Suicidal thoughts and actions (including suicide)
• Tremor
• Trouble sleeping
• Increase in certain white blood cells (eosinophils) and possible inflamed blood vessels throughout the body (systemic vasculitis). Rarely, this can happen in people with asthma who take montelukast sodium tablets. This sometimes happens in people who also take a steroid medicine by mouth that is being stopped or the dose is being lowered.

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

2.1.1 Determining Settings of Care

The IMS Health, National Sales Perspectives™ database (see Appendix C for full database description) was used to determine the various retail and non-retail channels of distribution for montelukast. Over the cumulative time period from March 2012 to September 2013, approximately 84% of montelukast bottles/packages were distributed to outpatient retail pharmacies; 11% were to mail-order/specialty pharmacies; and 5.5% were to non-retail settings. As a result, outpatient retail pharmacy utilization patterns were examined. Mail-order/specialty and non-retail pharmacy settings were not included in this analysis.

2.1.2 Data Sources Used

Proprietary drug utilization databases were used to conduct this analysis (see Appendix C for full database description).

The IMS Health, Vector One®: Total Patient Tracker (TPT) database was used to obtain the nationally estimated number of patients receiving dispensed prescriptions for montelukast, stratified by patient age (0-1, 2-5, 6-11, 12-16, and 17+ years), from U.S. outpatient retail pharmacies from March 1, 2012 to September 30, 2013, cumulative. The top 10 physician specialties prescribing montelukast were obtained from the IMS Health, National Prescription Audit™ (NPA) database. The top 5 diagnoses associated with the use of montelukast,

stratified by patient age (0-1, 2-5, 6-11, 12-16, and 17+ years), were obtained from Encuity Research, LLC., TreatmentAnswers with Pain Panel database.

2.2 RESULTS

2.2.1 Patient Demographics

Table 1 below provides the number of patients receiving dispensed prescriptions for montelukast, stratified by patient age, from the U.S. outpatient retail pharmacies. Over the cumulative time period from March 2012 to September 2013, approximately 8.8 million patients received dispensed prescriptions for montelukast. Adult patients aged 17 years and older accounted for approximately 62.5% (5.5 million patients) of total patients. Pediatric patients aged 0-16 years old accounted for approximately 38% (3.3 million patients) of total patients. Of these pediatric patients, 47% were aged 6-11 years. Patients aged 0-1 years old (201,000 patients), 2-5 years old (956,000 patients), and 12-16 years old (872,000 patients) accounted for approximately 6%, 29%, and 26%, respectively, of total pediatric patients.

Table 1. Nationally estimated number of patients receiving dispensed prescriptions for montelukast, stratified by patient age*, from U.S. outpatient retail pharmacies, cumulative March 2012 to September 2013

	Cumulative 3/2012-9/2013	
	N	%
Total montelukast	**8,798,502**	***100.00%***
0 - 16 years	3,307,328	*37.59%*
0 - 1 years	200,588	*6.06%*
2 - 5 years	955,779	*28.90%*
6 - 11 years	1,562,665	*47.25%*
12 - 16 years	872,092	*26.37%*
17+ years	5,500,621	*62.52%*
Unknown Age	2,232	*0.03%*

Source: IMS Health, Vector One®: Total Patient Tracker. March 2012 to September 2013. Data extracted May 2014. Files: TPT 2014-585 montelukast PAC age 5-5-2014.xlsx; TPT 2014-585 montelukast PAC 0-16 age 5-6-2014.xlsx

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0 - 16 years includes patients aged 16 years and 11 months.

**Summing patients across patient age bands will result in double counting and overestimates of patient counts. Moreover, the sum of the percentages will be greater than 100% because patients are double counted across age bands.

2.2.2 Top 10 Prescribing Specialties

Table 2 below provides the number of dispensed prescriptions for montelukast, stratified by the top 10 prescribing specialties, from U.S outpatient retail pharmacies. Over the cumulative time period from March 2012 to September 2013, approximately 40.8 million prescriptions were dispensed for montelukast. General Practice/Family Medicine/Doctor of Osteopathic specialists accounted for the highest proportion of total dispensed prescriptions for montelukast at approximately 30% (12.1 million prescriptions). Pediatricians and Internal Medicine specialists followed at approximately 18% (7.2 million prescriptions) and 16% (6.4 million prescriptions), respectively, of total montelukast dispensed prescriptions.

Table 2. Nationally estimated number of prescriptions dispensed for montelukast, stratified by top 10 prescribing specialties, from U.S. outpatient retail pharmacies, cumulative March 2012 to September 2013

	Cumulative 3/2012-9/2013	
	TRx	%
Total montelukast	**40,838,635**	***100.0%***
Family Practice/General Practice/Doctor of Osteopathy	12,093,806	*29.6%*
Pediatrician	7,211,482	*17.7%*
Internal Medicine	6,409,840	*15.7%*
Allergy/Immunology	3,860,951	*9.5%*
Nurse Practitioner	3,273,081	*8.0%*
Pulmonary Diseases	2,348,633	*5.8%*
Physician Assistant	1,910,595	*4.7%*
Otolarynology	1,123,578	*2.8%*
Unspecified	818,350	*2.0%*
Emergency Medicine	154,575	*0.4%*
Others	1,633,744	*4.0%*

Source: IMS Health, National Prescription Audit™. March 2012 to September 2013. Data extracted May 2014. Files: NPA 2014-585 montelukast PAC specialty 5-5-2014.xlsx; NPA 2014-585 montelukast PAC top 10 specialty 5-5-2014.xlsx

2.2.3 Diagnoses Associated with Montelukast Use

Diagnoses (in terms of drug use mentions[3]) associated with the use of montelukast, stratified by patient age, from March 2012 to September 2013, cumulative, were coded according to the International Classification of Diseases (ICD-9-CM) and 95% confidence intervals were applied to the estimates (Table 3). "Asthma" (ICD-9 code 493) was the top diagnosis associated with the use of montelukast for all patient age groups. "Asthma" accounted for approximately 48-58% of uses, depending on patient age.

"Allergic Rhinitis" (ICD-9 code 477) was the second most mentioned diagnosis associated with the use of montelukast for all patient age groups. "Allergic Rhinitis" accounted for approximately 24-29% of uses, depending on patient age.

Table 3. Diagnoses associated with the use of montelukast, stratified by patient age, as reported from U.S. office-based physician practices, cumulative March 2012 to September 2013

	Cumulative 3/2012-9/2013		
	Uses	%	(95% CI)
Total montelukast	**9,680,000**	***100.0%***	**(9,209,000 - 10,152,000)**
0-1 years	202,000	*2.1%*	(134,000 - 270,000)
493 ASTHMA	97,000	*48.1%*	(50,000 - 145,000)
477 ALLERGIC RHINITIS	51,000	*25.1%*	(17,000 - 85,000)
486 PNEUMONIA, ORGANISM NOS	16,000	*7.9%*	(<500 - 35,000)
473 CHRONIC SINUSITIS	13,000	*6.5%*	(<500 - 30,000)
472 CHR PHARYNG/NASOPHARYNG	8,000	*3.8%*	(<500 - 21,000)
All Others	17,000	*8.6%*	(<500 - 37,000)
2-5 years	694,000	*7.2%*	(568,000 - 821,000)
493 ASTHMA	354,000	*51.0%*	(264,000 - 444,000)
477 ALLERGIC RHINITIS	177,000	*25.5%*	(113,000 - 241,000)
786 RESP SYS/OTH CHEST SYMP	61,000	*8.8%*	(24,000 - 99,000)
478 OTH UPPR RESPIRATORY DIS	19,000	*2.7%*	(<500 - 40,000)
472 CHR PHARYNG/NASOPHARYNG	12,000	*1.7%*	(<500 - 29,000)
All Others	71,000	*10.2%*	(31,000 - 112,000)
6-11 years	1,530,000	*15.8%*	(1,342,000 - 1,717,000)
493 ASTHMA	861,000	*56.3%*	(721,000 - 1,002,000)
477 ALLERGIC RHINITIS	444,000	*29.0%*	(343,000 - 545,000)
995 CERTAIN ADVERSE EFF NEC	50,000	*3.3%*	(16,000 - 84,000)
786 RESP SYS/OTH CHEST SYMP	40,000	*2.6%*	(10,000 - 71,000)
473 CHRONIC SINUSITIS	33,000	*2.1%*	(5,000 - 60,000)
All Others	101,000	*6.6%*	(53,000 - 150,000)
12-16 years	740,000	*7.7%*	(610,000 - 870,000)
493 ASTHMA	426,000	*57.6%*	(327,000 - 525,000)
477 ALLERGIC RHINITIS	180,000	*24.3%*	(116,000 - 244,000)
995 CERTAIN ADVERSE EFF NEC	49,000	*6.7%*	(16,000 - 83,000)
473 CHRONIC SINUSITIS	17,000	*2.4%*	(<500 - 37,000)
786 RESP SYS/OTH CHEST SYMP	16,000	*2.1%*	(<500 - 35,000)
All Others	51,000	*6.9%*	(17,000 - 85,000)
17+ years	6,259,000	*64.7%*	(5,879,000 - 6,638,000)
493 ASTHMA	3,110,000	*49.7%*	(2,843,000 - 3,377,000)
477 ALLERGIC RHINITIS	1,644,000	*26.3%*	(1,450,000 - 1,838,000)
995 CERTAIN ADVERSE EFF NEC	348,000	*5.6%*	(259,000 - 437,000)
786 RESP SYS/OTH CHEST SYMP	298,000	*4.8%*	(215,000 - 380,000)
496 CHR AIRWAY OBSTRUCT NEC	244,000	*3.9%*	(169,000 - 319,000)
All Others	614,000	*9.8%*	(495,000 - 733,000)
Unknown Age	255,000	*2.6%*	(179,000 - 332,000)

Source: Encuity Research, LLC., TreatmentAnswers™. March 2012 to September 2013. Data extracted May 2014. File: PDDA 2014-585 montelukast PAC dx3 age 5-5-2014.xlsx

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

The FAERS database was searched with the strategy described in Table 3.1.1[4]. See Appendix D for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy

Date of search	May 13, 2014
Time period of search	March 26, 2012* - September 26, 2013
Product active ingredient	Montelukast, Montelukast sodium

Search Parameters	Ages: all ages; Outcomes: all outcomes; Country: foreign and domestic

[*] Approval date of latest pediatric labeling

3.2 RESULTS

3.2.1 Total Number of FAERS Cases by Age

Table 3.2.1 Total adult and pediatric FAERS cases* March 26, 2012 through September 26, 2013 with montelukast.

	All reports (US)	Serious[†] (US)	Death (US)
Adults (≥ 17 years)	1148 (905)	915 (674)	75 (60)
Pediatrics (0 - < 17years)	731 (579)	**570 (422)**	5[§] (5)

**** May include duplicates and transplacental exposures, and have not been assessed for causality***

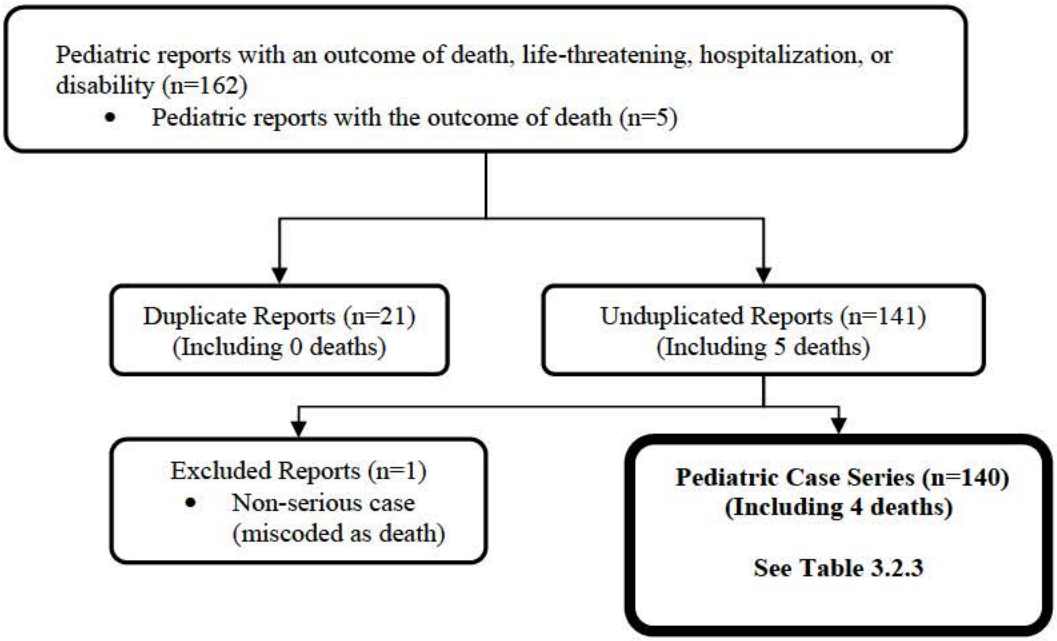
† Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

[§] No additional cases of pediatric deaths were identified among cases not reporting an age.

3.2.2 Selection of Serious Pediatric Cases in FAERS

Of the 570 serious pediatric reports, 162 reported an outcome of death, life-threatening, hospitalization, or disability (See Table 3.2.1)[5]. **Figure 3.2.2** summarizes the specific selection of cases to be summarized in **Sections 3.3 and 3.4.**

Figure 3.2.2 Selection of Serious Pediatric Cases with Montelukast from March 26, 2012 through September 26, 2013



3.2.3 Characteristics of Pediatric Case Series

Appendix E lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

Table 3.2.3 Characteristics of Pediatric Case Series with Montelukast (N=140)

Age	0 - < 1 month	0
	1 month - < 2 years	7
	2 - < 6 years	36
	6 - < 12 years	57
	12 - < 17 years	40
Sex	Male	77
	Female	62
	Unknown	1
Country of reporter	United States	98
	Foreign	42
Reported indication	Asthma	65
	Unknown	31
	Allergies	12
	Asthma and allergies	7
	Hypersensitivity	4
	Wheezing	3
	Allergies and cough	2

Table 3.2.3 Characteristics of Pediatric Case Series with Montelukast (N=140)		
	Bronchitis	2
	Respiratory disorder	2
	Rhinitis	2
	Rhinitis and asthma	2
	Bronchial hyperreactivity	1
	Dermatitis atopic	1
	Eczema	1
	Gastric disorder	1
	Lung disorder	1
	Off-label use	1
	Rhinitis and sinusitis	1
	Upper respiratory tract infection	1
Serious Outcome*	Death	4
	Life-threatening	45
	Hospitalization	81
	Disability	33

* Subset of serious pediatric reports with an outcome of death, life-threatening, hospitalization, or disability. A report may have one or more outcome.

3.3 SUMMARY OF PEDIATRIC DEATHS (N=4)

The FAERS database contained four pediatric cases with an outcome of death in association with montelukast use from March 26, 2012 through September 26, 2013. All cases were US reports. Summary of narratives of the deaths are found below.

Case # 9006984, 2013: A consumer report of a 2-year-old male who received montelukast 4 mg (mixed with water, juice, or milk) at bedtime for asthma. The patient experienced aggression, crying, ear pain, gait disturbance, insomnia, and pyrexia. The report indicated that one or more of the events resulted in death. The patient began to have a very high fever shortly after he was given montelukast at bed time. The doctor advised the mom to discontinue the medication for 5 days and try again. The mom waited 5 days and restarted the medication and the patient complained of an earache and became "real wobbly-almost like a drunk and whiny." Over the next few days, the medication was continued "because the doctors said he really needed it and he may have to get used to it." However, the same adverse events were re-occurring. The mom stopped the medication and contacted the doctor to prescribe another medication. "The doctor claims it is supposed to help him sleep better but the patient continues the crying, whiny and fighting within 15 min after taking montelukast sodium." No further information was available.

Case # 9010584, 2013: A 16-year-old male was placed on therapy with montelukast 10 mg once a day for the treatment of allergies and asthma. The patient was a healthy, active and

involved student in high school. He had his annual physical on an unspecified date (result unknown) and the patient's medications included fluticasone propionate/salmeterol xinafoate, montelukast 10mg (as needed), and albuterol (as needed during strenuous exercise). The last montelukast prescription was filled on 17-Apr-2006. Therapy with montelukast was discontinued on 21-Aug-2006. On [redacted], the patient committed suicide after taking montelukast for approximately 3 years.

Case # 9108560, 2013: A physician's assistant report of a 12-year-old female who had no history of depression and started therapy with Singulair 5mg for asthma and allergic rhinitis. The patient started therapy with brand Singulair approximately 3 or 4 years ago; she experienced mood changes after taking generic montelukast. She was irritable, moody, had trouble sleeping, and had a "bad attitude." She was also taking fluticasone propionate/salmeterol xinafoate but it was discontinued and the patient was placed back on brand Singulair in combination with a long acting beta agonist (LABA) with some improvement in mood. It was reported that the patient was non-compliant and the behavioral changes did not abate after stopping the drug. The cause of death was reported as suicide.

Case # 9277389, 2013: A pharmacist report of a 9-year-old male with no history of depression/mood disorders died from an apparent self-inflicted gunshot wound. The patient had been taking montelukast 5mg for approximately 7 ½ years. Montelukast was the only maintenance medicine that the patient had been taking. No further information was provided.

Reviewers Comment: Overall, these cases reported labeled neuropsychiatric adverse events (aggression, behavioral changes, and suicide) that are listed in the Warnings and Precautions section of the labeling. The cause of death was unknown in the case of the 2-year-old male (Case # 9006984).

3.4 SUMMARY OF ADVERSE EVENT REPORTS WITH AN OUTCOME OF LIFE-THREATENING, HOSPITALIZATION, OR DISABILITY (N=136)

Cases in this section are categorized by Preferred Terms that best represent the reported adverse event(s). Preferred terms are then grouped by like terms and organized by System Organ Class.

3.4.1 Psychiatric Disorders (N=74)

Labeled Event(s) in the Warnings and Precautions, Adverse Reactions, and Patient Counseling sections: Aggression/Anxiety/Depression/Hallucination/Sleep disorder/Sleep terror/Suicidal ideation/Suicidal behaviour/Suicide attempt /Self injurious behaviour

Aggression (n=8)

Eight cases reported aggression in males (n=6) and females (n=2). The median age was 12 years, with a range of 10 years to 15years. Two patients reported time to onset, one patient reported that the event occurred within two weeks of starting therapy and the other patient reported that the event occurred 20 days after starting montelukast. One case reported a positive rechallenge and one case reported a positive dechallenge. In the positive rechallenge case, the patient was hospitalized in the psychiatry department. Four of the eight patients considered the event to be disabling.

Anxiety (n=2)

One case involved a 24-month-old female who experienced extreme anxiety within two days of taking montelukast. Another case was of an 8-year-old male who had been taking montelukast for two years and experienced anxiety which triggered his tics.

Depression (n=4)

Four cases reported depression in 3 females and 1 male with a median age of 5 years, ranging from 2 to 14 years. The time to onset of the event ranged from "immediate" to 7 years. The patient with the 7-year onset had a history of depression. Montelukast was discontinued and the events resolved in three patients and improved in one patient.

Hallucination (n=10)

Of the ten cases of hallucination, one case reported visual hallucination and two cases reported night hallucination. There were 4 females and 6 males with a median age of 6 years, ranging from 3 to 14 years. Eight cases reported hospitalization. Four cases documented a time to onset ranging from 11 days to "within the same year." One case reported a medical history of bipolar disorder. In one case, hallucination occurred temporal to montelukast dose increase (from 5mg to 10mg daily). Five cases reported symptom abatement upon the discontinuation of montelukast (positive dechallenge).

Sleep disorder (n=1)/Sleep terror (n=2)

A 7-year-old female with a history of night terrors triggered by the use of montelukast presented to the hospital after falling through the attic door in her house while sleep walking. She was admitted to the hospital due to the injury and the outcome was not reported. The remaining two patients, 5 and 6 year old females, experienced sleep terror and sleep disturbance, and had symptom resolution after montelukast discontinuation.

Suicidal ideation (n=27)/Suicidal behaviour (n=1)/Suicide attempt (n=7)/Self injurious behaviour (n=2)

Thirty-seven cases of suicidal ideation, suicidal behavior, suicide attempt, or self injurious behavior were identified in our case series. There were 18 females and 19 males with a median age of 11 years, ranging from 4 to 16 years. Eighteen patients reported a time to onset of event as immediately (n=3), days (n=3), months (n=4), and years (n=8). Fifteen cases reported hospitalization. Two cases reported suicidal ideation after montelukast dose was increased from 4mg to 5mg and from 5mg to 10mg daily. One case reported a family history of behavioral disturbances. Among the 15 cases that reported montelukast discontinuation, four reported symptoms resolution. The cases of suicide attempt included overdose with acetaminophen (n=1), overdose with ibuprofen (n=1), "break[ing] up with girlfriend" (n=1), and defenestration due to family conflict (n=1). There were two cases of Self injurious behavior (PT). One case was of a 6-year-old female who tried to hurt herself two days after starting montelukast; the patient discontinued the medication but the outcome was not reported. The other case was of a 13-year-old male who was on montelukast and began cutting to ease the pain; the behavior stopped as soon as montelukast was discontinued.

<u>Narratives of select suicidal ideation, suicidal behaviour, suicide attempt, and self injurious behaviour cases:</u>

"My 13-year-old daughter has always been a friendly fun-loving, very social girl. She has been on Singulair -and in the more recent past the generic - for at least 8 years for control. Since last summer -summer of 2012-, she started getting very moody, agitated, difficult and

*generally unpleasant. As the months went on, that turned to depression, anxiety and then **suicidal ideations**. This is a straight "A" student with everything in the world going her way, loving and supportive family, tons of friends, etc. The anxiety and depression worsened, as did the suicidal ideations, and major self-loathing. We took her to therapist, then to a psychiatrist for months. It got so bad that we were told by everyone working with her that she had to be pulled from school, 5 weeks before she was finished, and admitted to an intense therapy program -therapeutic boarding school- for her issues. In May -just before she had to go- she was increased from the 5 mg she had been taking for 8 years to 10 mg… I took her to a new Pediatric Pulmonologist there. He told me -without knowing she had depression/anxiety- that if I didn't think the Singulair made a huge difference, he would recommend taking her off be it can cause depression!"*

*"A 4-years-old male patient started therapy with montelukast sodium (manufacture unknown) (dose, duration, indication and lot number not provided). No other co-suspects were reported. No concomitant medications were reported. On an unknown date the patient experienced **suicidality**, he was going to kill himself, walked around house with rope around his neck and mood incongruent. The outcome of suicidality, he was going to kill himself, walked around house with rope around his neck and mood incongruent was unknown."*

*"A 10-year-old male patient treated with montelukast sodium experienced anxiety, conversion disorder, decreased appetite, depression, sleep disorder, and **suicidal ideation**. The listing indicated that one or more of the events required hospitalization and required intervention to prevent permanent damage/impairment. No further information is available.*

*"A 15-year-old female with hypersensitivity (no detail) who was placed on therapy with montelukast sodium, 10 mg tablet, once a day for the treatment of allergic asthma (duration not reported). There was no concomitant medication. In October 2011, after a few months treatment with montelukast the patient experienced depressive state and attempted suicide. After a new clinical evaluation, drug treatment was implicated. In December 2011, therapy with montelukast sodium was discontinued and replaced with beclometasol + formoterol (Innovair). The patient's depressive state and **attempted suicide** persisted."*

"A 12-year-old female started therapy with montelukast sodium 5 mg daily in Dec-2004, and then received montelukast sodium 10 mg daily on an unknown date for asthma. No other co-suspects were reported. No concomitant medications were reported. On (b) (6) *, the patient experienced **suicide attempt** by defenestration (hospitalization, medically significant and life threatening) in the context of family conflict. There were few secondary physical sequelae. Montelukast sodium was discontinued in Sep-2012. The patient was followed in a youth center. The outcome of suicide attempt is recovering."*

*"A 14-year-old male patient who on 03-Apr-2011 was placed on montelukast sodium, tablet, (Lot# E010166, Exp. 31-Jul-2013, twice a day, orally), dose not reported for the treatment of asthma. On an unspecified date the patient experienced agitation, insomnia, aggression, nervousness, screaming and **suicidal behaviour**. The listing indicated that*

one or more of the events was considered to be immediately life-threatening. The therapy with montelukast sodium was discontinued on 09-Apr-2011. No further information is available."

"A 13-year-old white male student was on montelukast sodium and developed fears and self injury type behaviour in February 2013. He began cutting to ease the pain. As soon as the montelukast sodium was stopped, the behaviour stopped. No treatment was given. On 01-Apr-2013, the patient recovered from fears and ***self injury*** *type behaviour. The outcome of pain was unknown."*

Unlabeled Event(s): Abnormal behavior/Obsessive-Compulsive disorder/Psychotic disorder/Tic/Tourette's disorder

Abnormal behavior (n=1)
A 3-year-old female who was taking montelukast for allergies experienced crying, wanting to be "baby" again and atypical behavior/emotional issues. The symptoms resolved within 4 days of discontinuing the medication.

Obsessive-Compulsive disorder (n=4)/Psychotic disorder (n=2)
Six cases of obsessive-compulsive disorder or psychotic disorder were identified in our case series. There were five males and one female with a median age of 7 years, ranging from 6 to 9 years. One patient was hospitalized in order to study the origin of the obsessive compulsive disorder. Three cases reported symptoms of obsessive-compulsive disorder, including a 9-year-old male "washing hands 30 to 60 times a day and being afraid of germs which he believed would kill him," a 6-year-old male who "experienced nightmare which lead to the development of an obsessive compulsive disorder," and a 7-year-old male who "obsessed with food's expiration dates." The psychotic disorder cases were nonspecific. A 15-year-old and 9-year-old male experienced psychotic disorder. Three cases reported a positive dechallenge.

Tic (n=1)/Tourette's disorder (n=2)
One case of tics was identified in our case series. A 2-year-old male developed various motor tics within 4-5 months after taking montelukast. The patient discontinued montelukast at approximately 8 years of age and tics decreased in intensity and frequency but did not resolve. The patient was diagnosed with a tic disorder at age 9. Two cases of Tourette's disorder were identified in our case series. One case involved a 9-year-old male who started therapy with montelukast. On an unknown date the patient experienced Tourette's disorder and was hospitalized. The outcome was unknown. The other case reported a 5-year-old male who started therapy with montelukast and on an unknown date experienced Tourette's disorder, abnormal dreams, excessive eye blinking, movement disorder, muscle twitching, onychophagia, rash, and tic requiring hospitalization. The outcome was unknown.

Reviewers Comment: Among the 74 cases of Psychiatric disorders, 10 described unlabeled events: Abnormal behavior, Obsessive-Compulsive disorder, Psychotic disorder, Tic, and Tourette's disorder. These 10 cases generally did not provide enough clinical information (such as the time to onset) for us to determine the relationship between the adverse event and montelukast. DPV will continue to monitor for unlabeled psychiatric disorders associated with montelukast use.

3.4.2 Nervous System Disorders (N=22)

Labeled Event(s): Convulsion/Epilepsy/Seizure/Muscle Spasm/Psychomotor hyperactivity/Tremor/Paraesthesia/Amnesia

"Seizures,""seizures (convulsions or fits)," "muscle aches," and "muscle cramps," are labeled events in the Adverse Reactions and Patient Counseling sections of the montelukast label. "Psychomotor hyperactivity" is labeled in the Overdosage section and "tremor" is labeled in the Warnings and Precautions and Patient Counseling Information sections of the montelukast label. Paraesthesia is labeled in the Adverse Reactions section of the montelukast label. "Memory impairment" is listed in the Warnings and Precautions and Adverse Reactions sections of the montelukast label.

Convulsion (n=6)/Epilepsy (n=1)/Seizure (n=2)

Nine cases of convulsion, epilepsy, or seizure were identified in our case series. There were 2 females and 7 males with a median age of 7 years, ranging from 2 to 14 years. Four types of seizures were reported: clonic convulsion, partial complex seizures, seizure anoxic, and febrile seizure. Seven cases reported hospitalization. The median time to onset of adverse event was 11 days, ranging from 3 days to 1 month (n=3). The symptoms included "patient quickly falling to the ground and fracturing skull," "patient experiencing unconsciousness," "patient choking and in a seizure, experienced fairly severe seizure that left patient paralyzed for nearly 45 minutes," "three episodes of febrile convulsions," "experienced a seizure in the shower," "experienced breath holding, convulsion, crying and seizure anoxic." In two cases, concomitant medications and medical history did not appear to be a contributing factor to the development of seizure. None of the cases reported a medical history of seizure. Five cases reported discontinuation of montelukast of which one case reported a positive dechallenge and one case a positive rechallenge.

Muscle Spasm (n=1)/Psychomotor hyperactivity (n=2)/Tremor (n=1)

Four cases of muscle spasm, psychomotor hyperactivity, or tremor were identified in our case series. There were three males and one female with a median age of 6 years, ranging from 4 to 10 years. The onset of symptoms ranged from 15 days to 7 months. Three cases reported hospitalization. The symptoms of muscle spasm included odd hand movements, constant finger playing with eye blinking, shoulder shrug and neck tics. The symptoms of psychomotor hyperactivity included psychomotor agitation and "hyper." One case reported that the patient was diagnosed with benign essential tremors. There was one positive dechallenge.

Paraesthesia (n=1)

A 13-year-old male with multiple allergies was placed on therapy with montelukast (strength, formulation and indication not reported). Approximately 5 minutes after montelukast administration, the patient experienced visual disturbance with metamorphopsia which lasted approximately 30 minutes, followed by right hand paresthesia, which lasted about 30 minutes; the patient was hospitalized. On the same day, therapy with montelukast was discontinued. The patient underwent a neurological examination and an electrocardiogram (results not available) and the patient started to recover from the adverse events.

Amnesia (n=1)

A 7-year-old male started therapy with montelukast and on an unknown date the patient experienced short-term memory loss. Other suspect therapies included salmeterol xinafoate. Concomitant medications and the outcome of the event were not reported.

Unlabeled Event(s): Abasia/Speech disorder/Excessive eye blinking/Intracranial pressure increased/Loss of consciousness/Neurologic symptoms/Vestibular disorder

Abasia (n=1)
A 4-year-old male was placed on therapy with montelukast for the treatment of asthma and seasonal allergies. No other co-suspect medications were reported. Concomitant medications included fluticasone propionate, salmeterol xinafoate and albuterol. He developed symptoms of knee pain and could not walk at 11 years of age. Therapy with montelukast was continued and the patient had not recovered from the events.

Speech disorder (n=1)
A 7-year-old male started therapy with montelukast for asthma. Other suspect therapies included quetiapine fumarate. Concomitant medications included fluticasone propionate and salmeterol xinafoate. On an unknown date the patient experienced speech disorder, gait disturbance, medication error, and somnolence which required hospitalization. Treatment information and the outcome of the events were unknown.

Excessive eye blinking (n=1)
A 7-year-old male was placed on therapy with montelukast for treatment of multiple allergies. The patient experienced excessive eye blinking on unspecified date. The action taken with montelukast was unknown. The case reported a positive rechallenge with montelukast. The outcome of the event was unknown and the event was reported to be disabling.

Intracranial pressure increased (n=1)
One case reported an 8-year-old male started therapy with montelukast. Other suspect therapies included loratadine, homeopathic medications (unspecified), beclomethasone dipropionate, and albuterol sulfate. No concomitant medications were reported. On an unknown date the patient experienced visual disturbance, eosinophil count and intracranial pressure increased. No treatment information was reported. The outcome of events was unknown.

Loss of consciousness (n=1)
A 12-year-old female started therapy with montelukast and within 5-10 minutes experienced loss of conscience, low pulse and paleness. The patient recovered from loss of conscience, low pulse and paleness five minutes later but immediately fainted again. Cardiac resuscitation had to be performed to the thorax area. The outcome of the event was not reported.

Neurologic symptoms (n=1)
A 5-year-old male was placed on therapy with montelukast 5 mg (total daily dose, duration and indication not reported) and "within the past month," the patient experienced neurological symptoms and was admitted to hospital for an unspecified duration and blood work results were normal. The therapy with montelukast sodium was discontinued and the status was not recovered.

Vestibular disorder (n=1)
A 15-year-old female patient on an unspecified date was placed on therapy with montelukast 10 mg (total daily dose, duration and indication not reported) and experienced nausea and vertigo. The patient was hospitalized with the diagnosis of neurovegetative dystonia with marked psychosomatic signs, and peripheral vestibular syndrome. The action taken with montelukast was unknown.

Reviewers Comment: There was one case each of the following unlabeled events: Abasia, Speech disorder, Excessive eye blinking, Intracranial pressure increased, Loss of consciousness, Neurologic symptoms, and Vestibular disorder. Overall, these reports did not provide relevant information (such as time to onset or outcome of the adverse event) for us to establish the relationship between the adverse events and montelukast. DPV will continue to monitor nervous system disorder events with montelukast use in pediatrics.

3.4.3 General disorders and administration site conditions (N=7)

Unlabeled Event(s): Adverse event/Drug ineffective/Product substitution issue/Reaction to drug excipient

Adverse event (n=1)

A 2-month-old female was placed on therapy with montelukast for an unspecified chronic pulmonary disorder on an unknown date. The patient was hospitalized for two weeks for an unspecified problem. No treatment information was reported. The action taken with montelukast and the patient's outcome was unknown.

Drug ineffective (n=1)

A 15-year-old male started therapy with montelukast. The other suspect therapies included albuterol, fluticasone propionate, loratadine, fluticasone propionate plus salmeterol xinafoate, omalizumab, ipratropium bromide and ranitidine. Concomitant medications were not reported. On an unknown date the patient experienced "drug ineffective and asthma" which required hospitalization. The treatment information was not reported. The outcome of the events was unknown.

Product substitution issue (n=4)

Four cases reported product substitution issues when switching from brand to generic. One case involved a 12-year-old female who had multiple asthma attacks nine days after brand Singulair 5mg was switched to generic montelukast. The second case involved a 6-year-old female who required daily use of a rescue inhaler and a steroid inhaler for 2 months while she was taking generic montelukast. Within three days of switching to brand Singulair, she was able to stop all inhalers and nebulizer treatments. The third case involved a 4-year-old female who started therapy with montelukast for asthma and other suspect medications and experienced product substitution issue. The case did not provide further information. The fourth case involved a 14-month-old female who was admitted to hospital with bronchiolitis for nine days. The patient was treated with Singulair sprinkles, which worked well and the patient improved. On an unknown date the patient was discharged from the hospital and Singulair was changed to montelukast. The patient's health deteriorated and was admitted to the hospital for coughing, worsening bronchiolitis, phlegm, and fever. The patient was re-admitted to the hospital for two and half days; she was treated with Singulair and her condition improved. On discharge, brand Singulair was switched back to generic montelukast and the patient started coughing and got sick again. Therapy with montelukast was discontinued and the outcome of the events was reported as recovered. The first case identified the manufacturer as Dr. Reddy's; however the other cases did not provide information on generic montelukast.

Reaction to drug excipient (n=1)

This is a case of a 13-year-old female who experienced lip swelling within 30 minutes of cetirizine ingestion. The generic cetirizine contains lactose and the patient has food allergies. Other suspect medications included fexofenadine and montelukast.

Reviewers Comment: Adverse event, Drug ineffective, Product substitution issue, and Reaction to drug excipient are unlabeled events. Many of the cases were confounded by concomitant medications or had insufficient clinical information. In the case of Reaction to drug excipient, the event occurred temporal to cetirizine administration; however montelukast also contains lactose. DPV will continue to monitor these events for increase in frequency of reports.

3.4.4 Hepatobiliary disorders (N=4)

Labeled Event(s) in the Adverse Reactions section: Hepatitis cholestatic/Liver injury/Pancreatitis

Hepatitis cholestatic (n=1)
A 10-year-old male on an unknown date started therapy with montelukast for bronchial hyperreactivity. The other suspect therapies included erythromycin and albuterol for pertussis. On an unknown date the patient experienced vomiting, general physical health deterioration, chromaturia, hepatitis cholestatic, jaundice, and ocular icterus requiring hospitalization. The outcome of events was unknown.

Liver injury (n=1)
A 4-year-old male was hospitalized for circumcision surgery and had taken montelukast sodium chewable tablet 4mg once daily for asthma for about several months before hospitalization. Concomitant drugs included fluticasone propionate and salmeterol xinafoate. Routine examination prior to surgery indicated that he suffered from liver injury with aspartate aminotransferase (AST) elevation about 10 times of upper limit. The outcome of the event and action taken with montelukast was unknown.

Pancreatitis (n=2)
One case involved a 10-year-old male who started therapy with montelukast 5 mg chewable tablet once daily. Concomitant therapies included albuterol sulfate. On an unknown date, the patient had symptoms of epigastric pain and vomiting and was admitted to the hospital. The patient's lipase levels were elevated and he was diagnosed with pancreatitis. The patient was treated with bowel rest and therapy with montelukast sodium was discontinued. The outcome of pancreatitis was reported as recovering. This case did not provide any pertinent medical history or drug reaction/allergy. The other case involved a 4-year-old male who started therapy with montelukast for bronchitis and tonsillitis and experienced pancreatitis. Other suspect therapies included cefixime. The outcome of the event and treatment information was unknown.

Reviewers Comment: There were a small number of reports for Cholestatic hepatitis, Hepatocellular liver-injury and Pancreatitis, which are all labeled events. DPV will continue postmarketing surveillance for these events.

3.4.5 Immune System Disorders (N=5)

Labeled Event(s) in Warnings and Precautions and Adverse Reactions section: Allergic granulomatous angiitis/Vasculitis

Allergic granulomatous angiitis (n=1)
A 14-year-old female started therapy with montelukast sodium for an unknown indication. Other suspect therapies included budesonide and corticosteroids. On an unspecified date, the patient experienced asthma and allergic granulomatous angiitis and was hospitalized. There was no reported treatment information and the patient's outcome was unknown.
Vasculitis (n=2)
The first case involved an 11-year-old female who was placed on therapy with montelukast 10 mg once a day for asthma. Concomitant medication included mometasone, ketotifen, and budesonide/dihydrated formoterol fumarate. The patient was hospitalized for bilateral pneumopathy with hypoxemia, alteration of the general condition, febricula, purpura of the ankles and of the elbows, arthralgia and polyneuritis. The patient was diagnosed as having Churg-Strauss syndrome and had not recovered. The second case involved a 6-year-old female who started therapy with montelukast for an unknown indication. Other suspect therapies included budesonide, albuterol, amoxicillin, cefaclor, and acetylcysteine. On an unknown date the patient experienced vasculitis, conjunctival hemorrhage and gastrointestinal hemorrhage requiring hospitalization. No treatment information was reported and the outcome of the events was unknown.

Unlabeled Event(s): Dermatitis exfoliative/Systemic lupus erythematosus

Dermatitis exfoliative (n=1)
A 9-year-old male started therapy with montelukast for atopic dermatitis and contact dermatitis. Concomitant medications included tacrolimus, mometasone furoate, cetirizine hydrochloride, fluticasone propionate/salmeterol xinafoate, and doxepin hydrochloride. On an unknown date the patient experienced exfoliative dermatitis and disease recurrence which required hospitalization. The outcome of the reported events was unknown.
Systemic lupus erythematosus (n=1)
A 14-year-old male started therapy with montelukast for an unknown indication. Other suspect therapies included desloratadine, clomipramine, and budesonide/formoterol fumarate. Concomitant medications were not reported. On an unknown date the patient experienced systemic lupus erythematosus. There was no reported treatment information and the patient's outcome was unknown.

Reviewers Comment: "Churg-Strauss syndrome" also known as allergic granulomatous angiitis is labeled in the Warnings and Precautions and Patient Counseling Information sections of the montelukast label. "Vasculitis" is a labeled event in the Warnings and Precautions, Adverse Reactions, and Patient Counseling Information sections of the label. The reports of Dermatitis exfoliative and Systemic lupus erythematosus are confounded by co-suspect medications. DPV will continue postmarketing surveillance of these events for increase in frequency of reports.

3.4.6 Respiratory, thoracic and mediastinal disorders (N=9)

Labeled Event(s): Bronchopneumonia/ Bronchospasm/ Upper respiratory tract infection/Wheezing

Bronchopneumonia (n=1)
An 18-month-old male started therapy with montelukast for an unknown indication and experienced suspicion of H1N1 influenza infection. On an unknown date the patient experienced bronchopneumonia, diarrhea, fever, and dyspnea requiring hospitalization. The therapy with montelukast was interrupted and the patient received oseltamivir phosphate due to suspicion of H1N1 influenza infection. The outcome of the events was reported as recovered/resolved. Therapy with montelukast was restarted and the events did not recur.
Bronchospasm (n=1)
A 34-month-old female developed a hypersensitivity reaction, worsening asthma, and pulmonary infiltration while on therapy with montelukast sodium chewable tablet 5 mg once a day for the treatment of asthma. Concomitant therapy included albuterol and cromolyn. A physician indicated that the patient took her first dose of montelukast in the office and was "fine." The physician reported that, after taking the dose of montelukast the next day, the patient's lips swelled and she had trouble breathing; therapy with montelukast was discontinued. The patient was hospitalized and treated with steroids, nebulizer treatments, and antibiotic therapy due to a possible infection. The patient subsequently recovered.
Upper respiratory tract infection (n=1)
A 2-year-old female started therapy with montelukast for asthma. Other suspect therapies included corticosteroids and fluticasone propionate/salmeterol xinafoate. Concomitant medications were not reported. On an unknown date the patient experienced upper respiratory tract infection which required hospitalization, adrenal suppression, asthma, gastroenteritis and hypoglycemic seizure. No treatment information was reported and the outcome of the events is unknown.
Wheezing (n=1)
A1-year-old male on an unspecified date started therapy with montelukast 4mg daily for wheezing. Secondary suspect therapies included fluticasone propionate. On an unknown date the patient experienced recurrent wheeze with recurrent hospitalization. Montelukast and fluticasone propionate were continued. The outcome was unknown and the patient was started on azithromycin. Medical history or concomitant medications were not reported.

Unlabeled Event(s): Obstructive airways disorder/Pulmonary tuberculosis/Respiratory failure/Apnoea

Obstructive airways disorder (n=1)
A 13-year-old male on an unspecified date was admitted to the intensive care unit for respiratory failure with conditions including allergic rhinitis and epilepsy. He was diagnosed with asthma attack and required mechanical ventilation. He was started on treatment with nasal budesonide, short-acting bronchodilators, formoterol, montelukast, and prednisolone. His disease progressed and required 24 hospitalizations for asthma and was started on omalizumab. Montelukast was held and his asthma was under control with regular use of budesonide and formoterol. The patient recovered with no return of symptom. The primary suspect drug was reported as budesonide.
Pulmonary tuberculosis (n=1)
A 9-month-old male started therapy with montelukast 4 mg granules daily for recurrent obstructive bronchitis. Concomitant therapies included budesonide. Concurrent conditions included family outbreak of tuberculosis. The infection also affected three other children of

the family who were not taking montelukast. The patient went to the emergency department due to fever and cough and was diagnosed with tuberculous pneumonia. Montelukast and budesonide were discontinued on hospital admission. The patient followed the antituberculous therapy and was recovering from tuberculous pneumonia. The physician reported that tuberculous pneumonia was due to a family outbreak of tuberculosis.

Respiratory failure (n=2)

The first case involved a 5-year-old female who presented with respiratory failure, jaundice, muscle weakness, vomiting and drowsiness 4 hours after she received a dose of varicella vaccine. The patient was allergic to eggs and cow protein and was being treated with montelukast 4 mg. The reporter considered montelukast as suspect drug due to the interaction. The patient was hospitalized on an unspecified date until she recovered. No further information was reported. The second case involved a 9-year-old female who started therapy with montelukast for asthma. Other suspect therapies included fluticasone propionate/salmeterol xinafoate. The patient experienced respiratory failure, asthma, asthmatic crisis, and cyanosis and was hospitalized. No treatment information was reported and the outcome of the events is unknown.

Apnoea (n=1)

A 7-month-old female was suffering from upper respiratory tract infection and was monitored at the hospital. The baby received a 4 mg sachet of montelukast oral granules 4mg daily for asthma. The patient suffered from acute apnea immediately after he aspirated the granules. The action taken with montelukast was unknown and the outcome was reported as recovered.

Reviewers Comment: "Pneumonia" and "Wheezing" are labeled in the Adverse Reactions section of the montelukast label. "Bronchospasm" is labeled in the Warnings and Precautions section of the label. "Upper respiratory tract infection" is labeled in the Adverse Reactions and Patient Counseling Information sections of the label. Obstructive airways disorder, Pulmonary tuberculosis, Respiratory failure, and Apnoea are unlabeled events. Many of these events can be attributed to the disease state. Pulmonary tuberculosis was a result of family outbreak of tuberculosis and one case of respiratory failure was confounded by exposure to varicella vaccine. DPV will continue postmarketing surveillance of these events for increase in frequency of reports.

3.4.7 Gastrointestinal Disorders (N=3)

Labeled Event: Vomiting

Vomiting (n=1)

A 9-year-old female started therapy with montelukast 5 mg at bedtime. Other suspect therapies included lansoprazole and salmeterol xinafoate. Concomitant medications included budesonide and albuterol. On an unknown date the patient experienced vomiting, cerebrovascular, coma, dizziness, drug interaction, headache, hemiplegia, and photosensitivity; the events resulted in hospitalization and disability. No treatment information was reported and the outcome of the event was unknown.

Unlabeled Event(s): Coeliac disease/Colitis

Coeliac disease (n=1)
A 5-year-old female with asthma and anemia started therapy with montelukast. Other suspect therapies included esomeprazole magnesium and iron supplement. Concomitant medications included prednisolone sodium phosphate and an infant formula (Neocate powder). On an unknown date, the patient experienced celiac disease and diarrhea. No treatment information was reported and the outcome of the events was unknown.
Colitis (n=1)
A 24-month-old female treated with montelukast experienced chills, clostridium difficile colitis, decreased appetite, diarrhea, fatigue, fungal infection, headache and rectal prolapse. The report indicated that one or more of the events was considered to be disabling and required intervention to prevent permanent damage/impairment. No further information was available.

Reviewers Comment: Vomiting is a labeled event in the Adverse Reactions, Overdosage, and Patient Counseling Information sections of the label. The celiac disease case was confounded by concomitant medications and the colitis case reported many adverse events without further information for us to determine a causal relationship. DPV will continue postmarketing surveillance of these events.

3.4.8 Skin and subcutaneous tissue disorders (N=1)

Unlabeled Event: Hair loss

Hair loss (n=1)
On an unknown date, a 12-week-old male infant started therapy with montelukast 4 mg daily orally for respiratory syncytial virus infection. Concomitant therapies included fluticasone, cholecalciferol, and sodium fluoride. The patient experienced hair loss at the temples and parietal, erythroderma in the diaper area with touch sensitivity and positive Nikolsky's sign. The patient was hospitalized and montelukast was discontinued. The outcome of the events was unknown.

Reviewers Comment: Hair loss is an unlabeled event. This single case did not provide relevant clinical information (such as time to onset or outcome of the event) for us to determine the relationship between hair loss and montelukast. DPV will continue to monitor for hair loss with montelukast.

3.4.9 Miscellaneous Events (N=2)

Unlabeled Event(s): Visual impairment/Fall

Visual impairment (n=1)
An 11-year-old male was placed on therapy with montelukast sodium, 5 mg chewable tablet, once daily for the treatment of asthma. Concomitant therapy included budesonide. Approximately 7 months after the onset of therapy, the patient experienced visual disturbance and headache and was hospitalized. Therapy with montelukast sodium continued and the visual disturbance and headache persisted. No further information is available.
Fall (n=1)
A 4-year-old female with rhinitis was placed on therapy with montelukast sodium, 4 mg oral sprinkles once a day for the treatment of asthma. Concomitant therapy included albuterol,

budesonide, loratadine, and mometasone furoate. Approximately two months after the onset of therapy, the patient experienced headache, language disorder and fall without trauma and was hospitalized. The therapy with montelukast sodium was discontinued and cerebral CT scan was performed and was normal. Subsequently, the patient recovered from the events.

Reviewers Comment: Visual impairment and Fall, are unlabeled events. These events are confounded by concomitant medications, lack of temporal association, and had small number of reports to establish a causal relationship between these events and montelukast. DPV will continue postmarketing surveillance of these events for increase in frequency of reports.

3.4.10 Vascular (N=3)

Unlabeled Event(s): Haematoma/Henoch-Schonlein purpura/post procedural haemorrhage

Haematoma (n=1)
A 6-year-old female started therapy with montelukast. The suspect therapies included esomeprazole, albuterol, and fluticasone propionate/salmeterol xinafoate. On an unknown date the patient experienced hematoma and decreased platelet adhesiveness requiring hospitalization. No treatment information was reported and the outcome of the events was unknown.

Henoch-Schonlein Purpura (n=1)
A 45-month-old male with a history of gastric reflux was placed on therapy with montelukast 4 mg chewable tablet once daily for the treatment of asthma. There was no concomitant medication. The patient's mother reported that her son had been experiencing Henoch-Schonlein purpura (HSP) since being on montelukast. The patient's mother said that "on some days the problem seemed to go away, but then would return the following day." The symptoms included abdominal pain, and swelling in all of his joints since being on montelukast. The patient was treated with prednisone and was hospitalized. Therapy with montelukast was discontinued two months after start of therapy and the patient's outcome was unknown.

Post procedural haemorrhage (n=1)
A 2-year-old female was operated for adenoidectomy with transtympanic drainage. The child received treatment with budesonide, montelukast 4 mg daily, and trimethoprim/sulfamethoxazole. Concomitant therapies included albuterol, acetaminophen, codeine, and amoxicillin. The child presented with a second bilateral amygdala bleeding post-tonsillectomy corresponding to a second episode of eschar falling off, which required the patient to return to the operating room. Bleeding was diffuse and abundant at tonsillar lodges and hemostasis was very laborious. Montelukast, budesonide, and albuterol were discontinued. The child was treated for the event and the outcome of postoperative hemorrhage and anemia was reported as recovering/resolving.

Reviewers Comment: Haematoma, Henoch-Schonlein purpura, and post procedural haemorrhage are unlabeled events. These events are confounded by concomitant medications and underlying diseases. Henoch-Schonlein Purpura is an unlabeled event however it is a form of vasculitis (a labeled event). DPV will continue postmarketing surveillance of these events.

3.4.11 Blood and lymphatic system disorders (N=3)

Labeled Event: Thrombocytopenia

Thrombocytopenia (n=1)
A 4-year-old male with lung and growth disorders received montelukast. Other suspect therapies included domperidone, budesonide, ipratropium bromide, captopril, and polyethylene glycol 4000. On an unknown date the patient experienced thrombocytopenia and lung disorder requiring hospitalization. No treatment information was reported and the outcome of the events was unknown.

Unlabeled Event(s): Burkitt's lymphoma stage II/Leukaemia

Burkitt's lymphoma stage II (n=1)
A 10-year-old male was enrolled in a study and initiated therapy with pimecrolimus 1% cream to treat atopic dermatitis. Five months later, the patient was diagnosed with Stage II Group B Ileocecal Burkitt's Lymphoma. Azathioprine, tacrolimus, and montelukast were co-suspect medications. The patient has a history of severe immune complications including a liver transplant. The Burkitt's lymphoma was in remission.
Leukaemia (n=1)
A 5-year-old male initiated therapy with montelukast chewable tablets (4/5 mg orally) two years ago for asthma. Concomitant medications included budesonide. On an unknown date the patient was diagnosed with leukemia. Two months after discontinuation of therapy, the patient experienced exercise induced bronchospasm and weakness. The patient was currently on chemotherapy (not specified). The outcome of leukemia was reported as recovering/resolving. The outcome of exercise induced bronchospasm and weakness was unknown. The reporting physician felt that there may be relation between montelukast sodium therapy and leukemia.

Reviewers Comment: Thrombocytopenia is a labeled event in the Adverse Reactions section of the montelukast label. Burkitt's lymphoma stage II and Leukaemia are unlabeled events. These events are confounded by concomitant medications, lack of temporal association, and had small number of reports to establish a causal relationship between these events and montelukast. DPV concludes no labeling revisions are warranted at this time.

3.4.12 Cardiac Disorders (N=2)

Unlabeled Event: Tachycardia

Tachycardia (n=2)
Two cases of tachycardia were identified in our case series. The first case involved a 10-year-old female who was placed on therapy with montelukast, 5 mg chewable tablet once a day for the treatment of asthma. The suspect therapies included desloratadine and fluticasone propionate/salmeterol. Four months after the initiation of montelukast, the patient experienced tachycardia, chest pain, vomiting, and was hospitalized. The therapies with montelukast, desloratadine, and fluticasone propionate/salmeterol were discontinued. Subsequently, the patient recovered from the events. The second case involved an 8-year-old female who started therapy with montelukast 5 mg daily for an unknown indication and respiratory disorder.

Other suspect therapies included desloratadine, terbutaline sulfate, salmeterol, and omalizumab. Concomitant medications included albuterol. On an unknown date the patient experienced tachycardia, headache, hot flush, muscular weakness, and paresthesia requiring hospitalization. No treatment information was reported and the outcome of the events was unknown.

Reviewers Comment: Tachycardia is an unlabeled event. The events were confounded by co-suspect medications or lacked a temporal association for us to determine the relationship between tachycardia and montelukast. DPV will continue postmarketing surveillance of these events.

3.4.13 Endocrine Disorder (N=1)

Unlabeled Event: Type I Diabetes mellitus

Type I Diabetes Mellitus (n=1)

An 8-year-old female started therapy with montelukast for an unknown indication. Other suspect therapies included cetirizine. No concomitant medications were reported. Thirty-four days after the onset of therapy, the patient experienced type 1diabetes mellitus requiring hospitalization. The outcome of the event was unknown.

Reviewers Comment: Type I Diabetes Mellitus is an unlabeled event. This case did not provide information on concomitant medication(s), underlying disease(s), and outcome of the event. DPV will continue routine pharmacovigilance of this event.

3.5 Additional Analyses

We also conducted a high level overview of 1) reports with an outcome of *other serious* that were received in the FAERS database from March 26, 2012 to September 26, 2013, and 2) reports received in the FAERS database from September 27, 2013 to March 27, 2014 to determine if there are additional serious unlabeled events that were not captured in our hands-on review of cases (Sections 3.3 and 3.4). The results of the overview showed that most of the reported events are either labeled or are related to the disease. The unlabeled events of interest that were not discussed in Sections 3.3 and 3.4 include Crying, Anger, Mood swings, Fear, Screaming, Mood altered, Personality change, Emotional disorder, Nervousness, Thinking abnormal, Feeling abnormal, Mental disorder, Affective disorder, Pain in Extremity, Panic attack, and Affect lability.

This overview uses crude counts of reports. The adverse events reported in these cases have not been assessed for an association with montelukast and may contain duplicate reports (see Appendices A and B, Tables 4 and 5).

3.5.1 Montelukast and Enuresis in Children

(b) (4)

(b) (4)

(b) (4)

Reviewer Comment:

(b) (4)

4 DISCUSSION

To provide context for the adverse event reports submitted to the FAERS database, drug utilization patterns for montelukast were assessed. Approximately 38% (3.3 million patients) of U.S. patients receiving dispensed prescriptions for montelukast were pediatric patients aged 0-16 years old. Although infrequent, off-label indications other than asthma and allergic rhinitis appear to be mentioned for all pediatric age groups.

Our analyses of montelukast drug utilization focused on only the outpatient retail pharmacies. Therefore, these estimates may not apply to other settings of care such as mail-order/specialty pharmacies and non-retail settings in which montelukast is used.

With interest in identifying rare, serious, or unlabeled events associated with montelukast use in the pediatric population, we reviewed pediatric cases for montelukast that had an outcome of death, life-threatening, hospitalization, or disability. The focus was for cases that were

received in the FAERS from March 26, 2012 (the date of latest pediatric labeling update) to September 26, 2013.

The review of the FAERS pediatric cases resulted in the identification of 140 serious cases, including four deaths. The majority of the pediatric cases reported neuropsychiatric events. Safety concerns have been raised and addressed by the FDA in the past regarding the increased risk of neuropsychiatric adverse events, including suicide and suicide attempts with the use of montelukast. However, there continues to be a lack of well-designed epidemiologic studies that can lead to the quantification of the suicide/suicide attempt risk level among patients using montelukast.

Overall, the four death cases reported labeled psychiatric adverse events (aggression, behavioral changes, and completed suicide) that are listed in the Warnings and Precautions section of the labeling. The cause of death was unknown in the case of the 2-year-old male (Case # 9006984). The majority of the non-fatal serious adverse events[6] are adequately described in the current labeling. No increased trend in severity or frequency of reporting of labeled events was noted.

There were a small number of reports for unlabeled events[7]; many events had one single report. Because of the overall small number of reports (compared to 3.3 million pediatric patients receiving dispensed prescriptions for montelukast in this time period), it was difficult to determine whether these reports documented new safety issues. Limitations to case interpretation include incomplete case descriptions or the paucity of clinical data the cases contain, underlying medical disorders, and confounders such as concomitant medications. DPV will continue postmarketing surveillance of these events.

5 CONCLUSION

Over the cumulative time period from March 2012 to September 2013, approximately 40.8 million montelukast prescriptions were dispensed and approximately 8.8 million patients received dispensed prescriptions for montelukast from U.S. outpatient retail pharmacies. Approximately 38% (3.3 million patients) were pediatric patients aged 0-16 years old. "Asthma" and "Allergic Rhinitis" were the two most common diagnoses associated with the use of montelukast for all pediatric age groups. This is consistent with the findings from the FAERS data summary which showed that asthma was the most frequently reported indication, followed by allergy-related indications. Although infrequent, off-label indications other than asthma and allergic rhinitis appear to be mentioned for all pediatric age groups.

We reviewed four post-marketing pediatric death cases and 136 non-fatal serious post-marketing cases (with an outcome of life-threatening, hospitalization, or disability) that were received in the FAERS database from March 26, 2012 to September 26, 2013. The pediatric safety profile described in these reports is consistent with the known safety profile and the current montelukast label. We did not identify any new safety concerns in children 0 to < 17 years old treated with montelukast.

6 RECOMMENDATIONS

DPV will continue postmarketing surveillance of all adverse events with the use of montelukast in the pediatric patients.

7 REFERENCES

1. Torjusen, Erica, MD, MHS. Singulair Allergy: Clinical Trial Data. FDA Nonprescription Drugs Advisory Committee meeting. May 2, 2014
2. Montelukast sodium Prescribing Information. Sandoz Inc. Princeton, NJ. Revised January 2014.
3. The term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.
4. As discussed at the planning meeting on April 29, 2014 with Office of Pediatric Therapeutics (OPT), we performed an additional search of reports that were received in the FAERS database from September 27, 2013 to March 27, 2014.
5. As discussed at the planning meeting on April 29, 2014 with Office of Pediatric Therapeutics (OPT), the focus of this review is reports with an outcome of death, life-threatening, hospitalization, and disability.
6. Labeled events include Aggression, Anxiety, Depression, Hallucination, Sleep disorders, Sleep terror, Suicidal ideation, Suicidal behaviour, Suicide attempt, Self injurious behaviour, Convulsion, Epilepsy, Seizure, Muscle Spasm, Psychomotor hyperactivity, Tremor, Paraesthesia, Amnesia, Hepatitis cholestatic, Liver injury, Pancreatitis, Allergic granulomatous angiitis, Vasculitis, Bronchopneumonia, Bronchospasm, Upper respiratory tract infection, Wheezing, Vomiting, and Thrombocytopenia.
7. Unlabeled events include Abnormal behavior, Obsessive-Compulsive Disorder, Psychotic Disorders, Self injurious behaviour, Tic, Tourette's Disorder, Abasis, , Speech disorder, Excessive eye blinking, Intracranial pressure increased, Loss of consciousness, Neurologic symptoms, Vestibular disorder, Adverse event, Drug ineffective, Product substitution issue, Reaction to drug excipient, Dermatitis exfoliative, Systemic lupus erythematosus, Obstructive airways disorder, Pulmonary tuberculosis, Respiratory failure, Apnoea, Coeliac disease, Colitis, Hair loss, Visual impairment, Fall, Burkitt's lymphoma stage II, Leukaemia, Haematoma, Henoch-Schonlein purpura, post procedural haemorrhage, Haematoma, Henoch-Schonlein purpura, Post procedural haemorrhage, Tachycardia, and Type I Diabetes mellitus.

8 APPENDICES

8.1 APPENDIX A. MEDDRA PTS FROM FAERS REPORTS WITH AN OUTCOME OF OTHER SERIOUS

Table 4. MedDRA PTs with N ≥ 10 from FAERS reports with an outcome of OT† in pediatrics for montelukast received by FDA from March 26, 2012 through September 26, 2013, sorted by decreasing number of FAERS reports per PT
Total Number of Reports*= 386

Row	MedDRA PTs	Number of Reports	Labeled^ (Yes/No), Location or Other Category
1	Aggression	118	Yes, W/P, AR, PCI labeled for aggressive behavior
2	Abnormal behaviour	115	No
3	Anxiety	77	Yes, W/P, AR, PCI labeled for anxiousness
4	Nightmare	57	Yes, W/P, AR, PCI labeled for dream abnormalities, bad or vivid dreams
5	Depression	56	Yes, W/P, AR, PCI
6	Crying	54	No
7	Insomnia	49	Yes, W/P, AR
8	Anger	44	No
9	Suicidal ideation	41	Yes, W/P, AR, PCI labeled for suicidal thinking and behavior, suicidal thoughts and actions
10	Agitation	38	Yes, W/P, AR, PCI
11	Hallucination	37	Yes, W/P, AR, PCI
12	Irritability	37	Yes, W/P, AR, PCI
13	Mood swings	37	No
14	Fear	36	No
15	Screaming	34	Yes, W/P, AR, PCI labeled for agitation
16	Mood altered	31	No
17	Headache	24	Yes, AR, OD, PCI
18	Depressed mood	23	Yes, W/P, AR, PCI labeled for depression
19	Product substitution issue	23	No
20	Sleep terror	22	Yes, W/P, AR, PCI labeled for dream abnormalities, bad or vivid dreams
21	Sleep disorder	21	Yes, W/P, AR, PCI labeled for dream abnormalities, insomnia, trouble sleeping, sleep walking
22	Fatigue	20	Yes, AR
23	Abnormal dreams	19	Yes, W/P, AR labeled for dream

Table 4. MedDRA PTs with N ≥ 10 from FAERS reports with an outcome of OT† in pediatrics for montelukast received by FDA from March 26, 2012 through September 26, 2013, sorted by decreasing number of FAERS reports per PT Total Number of Reports*= 386			
			abnormalities
24	Disturbance in attention	19	Yes, W/P, AR, PCI
25	Psychomotor hyperactivity	18	Yes, OD
26	Abdominal pain upper	17	Yes, AR, OD, PCI labeled for abdominal pain, stomach pain
27	Restlessness	17	Yes, W/P, AR, PCI
28	Convulsion	16	Yes, PCI
29	Drug ineffective	16	U
30	Personality change	16	No
31	Dyspnoea	15	DR
32	Emotional disorder	15	No
33	Cough	14	Yes, AR, PCI
34	Nervousness	14	No
35	Obsessive-compulsive disorder	14	No
36	Tic	14	No
37	Asthma	13	IR
38	Educational problem	13	Yes, W/P, AR labeled for disturbance in attention, memory impairment
39	Hallucination, visual	13	Yes, W/P, AR, PCI labeled for hallucinations
40	Thinking abnormal	13	No
41	Feeling abnormal	12	No
42	Mental disorder	12	No
43	Tremor	12	Yes, W/P, AR, PCI
44	Vomiting	12	Yes, AR, OD, PCI
45	Affective disorder	11	No
46	Diarrhoea	11	Yes, AR, PCI labeled for diarrhea
47	Rash	11	Yes, W/P, AR, PCI
48	Rhinorrhoea	11	Yes, AR,
49	Somnambulism	11	Yes, W/P, AR
50	Somnolence	11	Yes, AR, OD
51	Decreased appetite	10	No
52	Middle insomnia	10	Yes, W/P, AR labeled for insomnia
53	Nausea	10	Yes, AR, PCI
54	Pain in Extremity	10	No
55	Panic attack	10	No
56	Poor quality sleep	10	Yes, W/P, AR, PCI labeled for dream abnormalities, insomnia, trouble sleeping, sleep walking

† Other serious important medical events

* May include duplicates

^ Definitions: W/P = Warnings/Precautions, AR = Adverse Reactions, OD = Overdosage, PCI = Patient Counseling Information, CM= Confounded by Concomitant Medications, DR = Disease-related, IR = Indication-related, U = Uninformative

8.2 APPENDIX B. MEDDRA PTS FROM SEPTEMBER 27, 2013 TO MARCH 27, 2014

Table 5. MedDRA PTS from FAERS reports with serious outcomes† in pediatrics for montelukast received by FDA from September 27, 2013 to March 27, 2014, sorted by decreasing number of FAERS reports per PT

Total Number of Reports*=73

Row	MedDRA PTs	Number of Reports	Labeled^ (Yes/No), Location or Other Category
1	Aggression	22	Yes, W/P, AR, PCI labeled for aggressive behavior or hostility
2	Cough	13	Yes, AR, PCI
3	Dyspnoea	11	Disease related
4	Fatigue	11	Yes, AR
5	Nightmare	11	Yes, W/P, AR, PCI labeled for dream abnormalities, bad or vivid dreams
6	Abnormal behaviour	10	No
7	Breath sounds abnormal	10	DR
8	Hallucination	10	Yes, W/P, AR, PCI
9	Treatment noncompliance	10	U
10	Abdominal pain	8	Yes, AR, OD, PCI
11	Product substitution issue	8	U
12	Screaming	8	Yes, W/P, AR, PCI labeled for agitation
13	Sleep disorder	8	Yes, W/P, AR, PCI labeled for dream abnormalities, insomnia, trouble sleeping, sleep walking
14	Anger	7	No
15	Crying	7	No
16	Fear	7	No
17	Dysarthria	6	No
18	Flatulence	6	No
19	Miller fisher syndrome	6	No, duplicate reports
20	Somnambulism	6	Yes, W/P, AR
21	Ataxia	5	No
22	Drug ineffective	5	U
23	Eczema	5	Yes, AR
24	Guillain-barre syndrome	5	No, duplicate reports
25	Sensory disturbance	5	No
26	Insomnia	4	Yes, W/P, AR
27	Off label use	4	Uninformative
28	Vomiting	4	Yes, AR, OD, PCI

Table 5. MedDRA PTS from FAERS reports with serious outcomes† in pediatrics for montelukast received by FDA from September 27, 2013 to March 27, 2014, sorted by decreasing number of FAERS reports per PT Total Number of Reports*=73			
29	Agitation	3	Yes, W/P, AR, PCI
30	Asthma	3	DR
31	Irritability	3	Yes, W/P, AR, PCI
32	Psychomotor hyperactivity	3	Yes, OD
33	Pyrexia	3	Yes, PCI labeled for fever
34	Wheezing	3	IR
35	Affect lability	2	No
36	Anxiety	2	Yes, W/P, AR, PCI labeled for anxiousness
37	Depression	2	Yes, W/P, AR, PCI
38	Diarrhoea	2	Yes, AR, PCI labeled for diarrhea
39	Headache	2	Yes, AR, OD, PCI
40	Malaise	2	No
41	Nausea	2	Yes, AR, PCI
42	Personality change	2	No
43	Rhinorrhoea	2	Yes, AR,
44	Sleep terror	2	Yes, W/P, AR, PCI labeled for dream abnormalities, bad or vivid dreams
45	Suicidal ideation	2	Yes, W/P, AR, PCI labeled for suicidal thinking and behavior, suicidal thoughts and actions
46	Thirst	2	Yes, OD
47	Tic	2	No
48	Urticaria	2	Yes, AR

† Serious adverse drug included: outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, and other serious important medical events. A report may have one or more outcomes.

* May include duplicates

^ Definitions: W/P = Warnings/Precautions, AR = Adverse Reactions, OD = Overdosage, PCI = Patient Counseling Information, CM= Confounded by Concomitant Medications, DR = Disease-related, IR = Indication-related, U = Uninformative

8.3 APPENDIX C. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

The data from the IMS Health, National Sales Perspectives™, database do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer to various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume that facilities purchase drugs in quantities reflective of actual patient use.

IMS, Vector One®: Total Patient Tracker (TPT)

The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

IMS Health, National Prescription Audit™ (NPA)

The National Prescription Audit (NPA™) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions in the United States. The NPA audit measures both what is prescribed by the physician and what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies.

NPA™ receives over 2.7 billion prescription claims per year, captured from a sample of the universe of approximately 57,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 80% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data are available on-line for 72- rolling months with a lag of 1 month.

Encuity Research, LLC., TreatmentAnswers™ with Pain Panel

Encuity Research, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of

diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Indications for montelukast use were obtained using a monthly survey of 3,200 office-based physicians. Although these data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, physician survey data are best used to identify the typical uses for the products in clinical practice. Results should not be overstated when nationally projected estimates of annual uses or mentions fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

8.4 APPENDIX D. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.5 APPENDIX E. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS

Case Number	Version Number	Manufacturer Control Number	Case Number	Version Number	Manufacturer Control Number
8481819	1		9007529	1	US-009507513-0901USA02172
8482809	1	US-MERCK-1203USA03172	9007545	1	US-009507513-0907USA03600
8492068	1	US-MERCK-1203USA03202	9007572	1	US-009507513-0907USA03602
8492732	1	US-MERCK-1203USA04540	9007782	1	US-009507513-0901USA02174
8493430	1		9007784	1	US-009507513-1012USA00458
8524053	1	FR-MERCK-1204FRA00082	9007832	1	US-009507513-1012USA00490
8528094	4	US-009507513-1203USA04538	9007871	1	US-009507513-0909USA03413
8531604	1		9007971	1	US-009507513-1012USA00802
8548001	1	GB-MERCK-1205USA00064	9009019	1	US-009507513-1012USA00480
8552792	1	GB-MERCK-1205USA00705	9009860	1	US-009507513-1004USA01813
8554097	1	DE-MERCK-1205DEU00016	9010584	1	US-009507513-0812USA00678
8561357	1	US-MERCK-1205USA01930	9011278	1	US-009507513-1301USA002129
8566006	5	US-009507513-1205USA02181	9012794	1	US-MERCK-1301USA003276
8595722	1	FR-MERCK-1206FRA00002	9012839	1	US-009507513-0907USA03607
8600220	1	FR-MERCK-1206FRA00005	9013085	1	US-009507513-1007USA03928
8605380	1	FR-MERCK-1206FRA00018	9013105	1	US-MERCK-1301USA001871
8611889	1		9013306	1	US-009507513-0909USA03405
8613419	1	US-MERCK-1205USA02875	9013309	1	US-009507513-1012USA00451
8613421	1	US-MERCK-1205USA02858	9013336	1	US-009507513-0909USA03406
8616335	1	US-MERCK-1204USA00414	9013434	1	US-009507513-1301USA001438
8634857	1		9013763	2	US-009507513-1012USA00468
8638707	2	DSA 57767 2012	9014049	1	US-009507513-1301USA003553
8643855	3	SK-009507513-1206USA04452	9014528	1	US-009507513-1301USA003457
8644543	1	US-MERCK-1206USA04552	9014563	1	US-009507513-1301USA002597
8668090	1		9014708	1	US-009507513-1301USA003626
8708041	2	FR-009507513-1208FRA001028	9014797	1	US-MERCK-1301USA003699
8715585	1	WAES 1106USA00018	9015299	1	US-009507513-1201USA04243
8739373	4	HN-009507513-1208HND006792	9015307	1	US-009507513-1301XAA004113

Case Number	Version Number	Manufacturer Control Number	Case Number	Version Number	Manufacturer Control Number
8747188	1	WAES 1106USA03137	9015586	1	US-009507513-1012USA00487
8747232	1	WAES 1104UAS00219	9015726	1	US-009507513-1301USA003481
8762946	1	(DR, Reddy)	9016388	1	US-009507513-1201USA04241
8796688	3	US-009507513-1209USA006554	9018746	1	US-009507513-1301USA004188
8797653	2	FR-009507513-1112FRA00024	9032213	1	US-009507513-0812USA00704
8805808	3	KW-009507513-1209KWT008729	9032946	3	ES-009507513-0709ESP00015
8816249	2	BG-009507513-1209BGR010721	9060256	1	
8833854	3	GB-009507513-1210GBR004273	9069179	1	2013AP000058
8838614	2	US-009507513-1210USA004771	9085753	1	ES-ROXANE LABORATORIES, INC.-2013-RO-00157RO
8839465	1		9090880	1	FR-MERCK-2001-08-2007
8845329	3	AT-009507513-1210AUT002933	9094500	1	US-009507513-0812USA00887
8845712	2	MX-009507513-1210MEX007790	9108560	3	US-009507513-1302USA008908
8846294	1	FR-009507513-1210FRA007572	9122012	1	US-009507513-1301USA003664
8855862	1		9123982	1	US-009507513-1007USA03891
8889851	2	AU-009507513-1211AUS002422	9152444	1	PT-009507513-1303PRT003147
8912832	3	ES-009507513-0611ESP00030	9212871	3	US-009507513-1304USA000636
8969758	2	ES-009507513-1212ESP004998	9234676	3	US-ASTRAZENECA-2013SE23616
8983626	1	DE-009507513-1212DEU008724	9266211	1	AU-009507513-1009USA00221
8988325	1		9266498	2	ES-009507513-1304ESP006444
8996746	1	US-009507513-00072000	9277389	1	
8997463	1	US-MERCK-1301USA000932	9291057	3	FR-009507513-1305FRA002243
8997577	1	US-009507513-00040679	9294952	1	
9001322	1	US-009507513-1301USA001892	9302123	1	IT-009507513-1305ITA011009
9001423	1	US-009507513-1301USA001247	9310732	2	CN-MERCK-1305CHN013853
9001659	1	US-009507513-1301USA001260	9335833	1	DE-009507513-1306DEU000947
9001660	1	US-009507513-1301USA002107	9365380	2	ZA-009507513-1306ZAF010022
9002219	1	US-MERCK-1301USA001188	9365740	2	US-009507513-1306USA010112
9002422	1	US-009507513-0307USA02169	9380220	1	
9002811	1	US-009507513-1301USA001157	9398762	1	BR-MERCK-1306BRA001136

Case Number	Version Number	Manufacturer Control Number	Case Number	Version Number	Manufacturer Control Number
9002833	1	US-009507513-1301USA001838	9413619	4	IT-009507513-1307ITA011005
9003175	1	US-009507513-1301USA001546	9414430	1	US-009507513-1307USA010662
9005964	1	US-009507513-0901USA02233	9414636	1	AU-009507513-1307AUS004934
9005976	1	US-009507513-1301USA001631	9423988	1	CH-009507513-1307CHE013937
9006159	1	US-009507513-0907USA03587	9454739	2	PT-MERCK-1308PRT004258
9006170	1	US-009507513-0907USA03592	9470082	2	
9006226	1	US-009507513-0907USA03758	9503854	1	
9006271	1	US-009507513-0901USA02198	9515428	1	PHHY2013BR097882
9006575	1	US-009507513-1012USA00683	9515786	1	CA-009507513-1309CAN004209
9006984	1	US-009507513-0909USA03262	9518473	1	RU-009507513-1309RUS004078
9007357	1	US-009507513-1301USA002499	9524973	1	
9007443	1	US-009507513-1301USA003042	9536110	1	CA-009507513-1309CAN006063
9007459	1	US-MERCK-1301USA003059	9536457	1	
9007505	1	US-009507513-0901USA02207			

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/s/

DIPTI KALRA
09/02/2014

TRACY M PHAM
09/02/2014
Drug use data were cleared for public release.

HINA S MEHTA
09/02/2014

EILEEN WU
09/03/2014

JUDY A STAFFA
09/03/2014

ROBERT L LEVIN
09/04/2014